

WHAT IS CLAIMED IS:

1. A stable respiratory dispersion for the pulmonary delivery of one or more bioactive agents comprising a suspension medium having dispersed therein a plurality of perforated microstructures comprising at least one bioactive agent wherein said suspension medium comprises at least one propellant and substantially permeates said perforated microstructures.

2. The stable respiratory dispersion of claim 1, wherein said propellant comprises a compound selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

3. The stable respiratory dispersion of claim 1 wherein said propellant is a hydrofluoroalkane propellant.

4. The stable respiratory dispersion of claim 3 wherein said hydrofluoroalkane propellant comprises 1,1,1,2-tetrafluoroethane.

5. The stable respiratory dispersion of claim 3 wherein said hydrofluoroalkane propellant comprises 1,1,1,2,3,3,3-heptafluoro-n-propane.

6. The stable respiratory dispersion of claim 1 wherein said perforated microstructures comprise a surfactant.

7. The stable respiratory dispersion of claim 6 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

8. The stable dispersion of claim 6 wherein said perforated microstructures comprise a poloxamer selected from the group consisting of poloxamer 188, poloxamer 407, and poloxamer 338.

9. The stable dispersion of claim 6 wherein said perforated microstructures comprise oleic acid or its alkali salt.

10. The stable respiratory dispersion of claim 6 wherein said surfactant comprises a lipid.

11. The stable respiratory dispersion of claim 10 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

12. The stable respiratory dispersion of claim 10 wherein said lipid is a phospholipid.

13. The stable respiratory dispersion of claim 12 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteoylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

14. The stable respiratory dispersion of claim 6 wherein said perforated microstructures comprise greater than about 10% w/w surfactant.

15. The stable respiratory dispersion of claim 14 wherein said surfactant comprises a phospholipid.

16. The stable respiratory dispersion of claim 14 wherein said surfactant comprises oleic acid or its alkali salt.

17. The stable respiratory dispersion of claim 1 wherein said suspension medium and said perforated microstructures have a refractive index differential of less than about 0.4.

18. The stable respiratory dispersion of claim 1 wherein said suspension medium and said perforated microstructures have a refractive index differential of less than about 0.3.

19. The stable respiratory dispersion of claim 1 wherein said perforated microstructures comprise hollow porous microspheres.

20. The stable respiratory dispersion of claim 19 wherein the microspheres comprise a surfactant.

21. The stable respiratory dispersion of claim 1 wherein the mean geometric diameter is between 1 and 5 μm .

22. The stable respiratory dispersion of claim 1 wherein the mean aerodynamic diameter is between 0.5 and 5 μm .

23. The stable respiratory dispersion of claim 1 wherein the mean aerodynamic diameter is between 1 and 3 μm .

24. The stable respiratory dispersion of claim 1 wherein said bioactive agent has a fine particle fraction following aerosolization of greater than 30%

25. The stable respiratory dispersion of claim 1 wherein said bioactive agent has a fine particle fraction following aerosolization of greater than 50%

26. The stable respiratory dispersion of claim 1 wherein the density of the suspended particles permeated with the suspension medium substantially matches that of the suspension medium.

27. The stable respiratory dispersion of claim 1 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

28. The stable respiratory dispersion of claim 1 wherein said bioactive agents are selected from the group consisting of steroids, bronchodilators and peptides.

29. The stable respiratory dispersion of claim 1 wherein said bioactive agents are selected from the group consisting of budesonide, fluticasone propionate, salmeterol, formoterol and DNase.

30. A system for the pulmonary administration of a bioactive agent comprising:
a fluid reservoir;
a metering valve operably associated with said fluid reservoir; and
a stabilized dispersion in said fluid reservoir wherein said stabilized dispersion comprises a suspension medium having dispersed therein a plurality of perforated microstructures comprising at least one bioactive agent wherein said suspension medium comprises at least one propellant and substantially permeates said perforated microstructures.

31. The system of claim 30 wherein said fluid reservoir comprises a pressurized aerosol container and wherein said metering valve is adapted to dispense a pharmaceutically acceptable amount of said bioactive agent in the form of an aerosol upon activation.

32. The system of claim 30, wherein said propellant comprises a compound selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

33. The system of claim 30 wherein said hydrofluoroalkane propellant comprises a hydrofluoroalkane propellant.

34. The system of claim 33 wherein said hydrofluoroalkane propellant comprises 1,1,1,2-tetrafluoroethane.

35. The system of claim 33 wherein said hydrofluoroalkane propellant comprises 1,1,1,2,3,3,3-heptafluoro-n-propane.

36. The system of claim 30 wherein said perforated microstructures comprise a surfactant.

5 37. The system of claim 36 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

38. The system of claim 36 wherein said surfactant comprises a lipid.

10 39. The system of claim 38 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

40. The system of claim 37 wherein said lipid is a phospholipid.

15 41. The system of claim 39 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylephosphatidylcholine and combinations thereof.

42. The system of claim 36 wherein said perforated microstructures comprise greater than about 10% w/w surfactant.

43. The system of claim 30 wherein said suspension medium and said perforated microstructures have a refractive index differential of less than about 0.4.

20 44. The system of claim 30 wherein said perforated microstructures comprise hollow porous microspheres.

45. The system of claim 30 wherein the mean geometric diameter of the perforated microstructures is between 1 and 5 μm .

25 46. The system of claim 30 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5 μm .

47. The system of claim 30 wherein said bioactive agent has a fine particle fraction following aerosolization of greater than 30%.

48. The system of claim 30 wherein the density of the suspended particles permeated with the suspension medium substantially matches that of the suspension medium.

30 49. The system of claim 30 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics,

leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

5 50. A method for forming a stabilized respiratory dispersion comprising the steps of:
 combining a plurality of perforated microstructures comprising at least one bioactive
 agent with a predetermined volume of suspension medium comprising at least one propellant to
 provide a respiratory blend wherein said suspension medium permeates said perforated
 microstructures; and

10 mixing said respiratory blend to provide a substantially homogeneous respiratory
 dispersion.

 51. A respiratory dispersion formed according to the method of claim 50.

 52. The method of claim 50 further comprising the step of spray drying an oil-in-
 water emulsion to provide said perforated microstructures wherein the disperse phase of said
15 emulsion comprises a fluorochemical.

 53. A respiratory dispersion formed according to the method of claim 52.

 54. The method of claim 52 wherein said fluorochemical has a boiling point of
 greater than about 60°C.

 55. The method of claim 50, wherein said propellant comprises a compound selected
20 from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane,
 perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

 56. The method of claim 50 wherein said propellant comprises a hydrofluoroalkane
 propellant.

 57. The method of claim 56 wherein said hydrofluoroalkane propellant comprises
25 1,1,1,2-tetrafluoroethane.

 58. The method of claim 56 wherein said hydrofluoroalkane propellant comprises
 1,1,1,2,3,3,3-heptafluoro-n-propane.

 59. The method of claim 50 wherein said perforated microstructures comprise a
 surfactant.

60. The method of claim 59 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

61. The method of claim 59 wherein said surfactant comprises a lipid.

5 62. The method of claim 61 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

63. The method of claim 61 wherein said lipid is a phospholipid.

64. The method of claim 62 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, 10 dipalmitoylphosphatidylcholine, distearylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

65. The method of claim 59 wherein said perforated microstructures comprise greater than about 10% w/w surfactant.

15 66. The method of claim 50 wherein said suspension medium and said perforated microstructures have a refractive index differential of less than about 0.4.

67. The method of claim 50 wherein said perforated microstructures comprise hollow porous microspheres.

68. The method of claim 50 wherein the mean geometric diameter of the perforated microstructures is between 1 and 5 μm .

20 69. The method of claim 50 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5 μm .

70. The method of claim 50 wherein said bioactive agent has a fine particle fraction following aerosolization of greater than 30%.

25 71. The method of claim 50 wherein the density of the suspended particles permeated with the suspension medium substantially matches that of the suspension medium.

72. The method of claim 50 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, 30 steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

73. A method for the pulmonary delivery of one or more bioactive agents comprising the steps of:

providing a pressurized reservoir containing a stabilized respiratory dispersion comprising a suspension medium having dispersed therein a plurality of perforated microstructures comprising one or more bioactive agents, wherein said suspension medium comprises a propellant and substantially permeates said perforated microstructures;

aerosolizing said respiratory dispersion by releasing pressure on the pressurized reservoir to provide an aerosolized medicament comprising said perforated microstructures; and administering a therapeutically effective amount of said aerosolized medicament to at least a portion of the pulmonary passages of a patient in need thereof.

74. The method of claim 73 wherein said pressurized reservoir is operably associated with a metering valve.

75. The method of claim 74 wherein said pressurized reservoir comprises a metered dose inhaler.

76. The method of claim 73, wherein said propellant comprises a compound selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

77. The method of claim 73 wherein said propellant comprises a hydrofluoroalkane propellant.

78. The method of claim 77 wherein said hydrofluoroalkane propellant comprises 1,1,1,2-tetrafluoroethane.

79. The method of claim 77 wherein said hydrofluoroalkane propellant comprises 1,1,1,2,3,3,3-heptafluoro-n-propane.

80. The method of claim 73 wherein said perforated microstructures comprise a surfactant.

81. The method of claim 80 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

82. The method of claim 80 wherein said surfactant comprises a lipid.

83. The method of claim 82 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

84. The method of claim 82 wherein said lipid is a phospholipid.

85. The method of claim 84 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, distearylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

86. The method of claim 80 wherein said perforated microstructures comprise greater than about 10% w/w surfactant.

87. The method of claim 73 wherein said suspension medium and said perforated microstructures have a refractive index differential of less than about 0.4.

88. The method of claim 73 wherein said perforated microstructures comprise hollow porous microspheres.

89. The method of claim 73 wherein the mean geometric diameter of the perforated microstructures is between 1 and 5 μm .

90. The method of claim 73 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5 μm .

91. The method of claim 73 wherein said bioactive agent has a fine particle fraction following aerosolization of greater than 30%.

92. The method of claim 73 wherein the density of the suspended particles permeated with the suspension medium substantially matches that of the suspension medium.

93. The method of claim 73 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

94. A method of increasing the effective pulmonary deposition of a bioactive agent using a metered dose inhaler comprising the steps of:

associating said bioactive agent with a plurality of perforated microstructures having a mean aerodynamic diameter of less than about 5 μm ;

dispersing said perforated microstructures in a suspension medium comprising a propellant to provide a respiratory dispersion; and

charging a metered dose inhaler with said respiratory dispersion wherein said charged metered dose inhaler provides a fine particle fraction of greater than approximately 20% w/w upon activation.

95. The method of claim 94 wherein said metered dose inhaler provides a fine particle fraction of greater than approximately 30% w/w upon activation.

96. The method of claim 94 wherein said metered dose inhaler provides a fine particle fraction of greater than approximately 50% w/w upon activation.

97. The method of claim 94, wherein said propellant comprises a compound selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

98. The method of claim 94 wherein said propellant comprises a hydrofluoroalkane propellant.

99. The method of claim 98 wherein said hydrofluoroalkane propellant comprises 1,1,1,2-tetrafluoroethane.

100. The method of claim 98 wherein said hydrofluoroalkane propellant comprises 1,1,1,2,3,3,3-heptafluoro-n-propane.

101. The method of claim 94 wherein said perforated microstructures comprise a surfactant.

102. The method of claim 101 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

103. The method of claim 101 wherein said surfactant comprises a lipid.

104. The method of claim 103 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

105. The method of claim 103 wherein said lipid is a phospholipid.

106. The method of claim 105 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteoylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

107. The method of claim 101 wherein said perforated microstructures comprise greater than about 10% w/w surfactant.

108. The method of claim 94 wherein said suspension medium and said perforated microstructures have a refractive index differential of less than about 0.4.

109. The method of claim 94 wherein said perforated microstructures comprise hollow porous microspheres.

5 110. The method of claim 94 wherein the mean geometric diameter of the perforated microstructures is between 1 and 5 μm .

111. The method of claim 94 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5 μm .

10 112. The method of claim 94 wherein the density of the suspended particles permeated with the suspension medium substantially matches that of the suspension medium.

113. The method of claim 94 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular agents, enzymes,
15 steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

114. A method for stabilizing a dispersion by reducing attractive van der Waals forces comprising the steps of:

providing a plurality of perforated microstructures;

20 combining the perforated microstructures with a suspension medium comprising at least one propellant wherein the suspension medium and the perforated microstructures are selected to provide a refractive index differential value of less than about 0.4.

115. A dispersion formed according to the method of claim 114.

25 116. The method of claim 114 wherein said refractive index differential value is less than about 0.3.

117. The method of claim 114, wherein said propellant comprises a compound selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

30 118. The method of claim 114 wherein said propellant comprises a hydrofluoroalkane propellant.

119. The method of claim 118 wherein said hydrofluoroalkane propellant comprises 1,1,1,2-tetrafluoroethane.

120. The method of claim 118 wherein said hydrofluoroalkane propellant comprises 1,1,1,2,3,3,3-heptafluoro-n-propane.

5 121. The method of claim 114 wherein said perforated microstructures comprise a surfactant.

122. The method of claim 121 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

10 123. The method of claim 121 wherein said surfactant comprises a lipid.

124. The method of claim 123 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

125. The method of claim 122 wherein said lipid is a phospholipid.

15 126. The method of claim 125 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylephosphatidylcholine and combinations thereof.

127. The method of claim 114 wherein said perforated microstructures comprise greater than about 10% w/w surfactant.

20 128. The method of claim 114 wherein said perforated microstructures comprise hollow porous microspheres.

129. The method of claim 114 wherein the mean geometric diameter of the perforated microstructures is between 1 and 5 μm .

25 130. The method of claim 114 wherein the mean aerodynamic diameter of the perforated microstructures is between 0.5 and 5 μm .

131. The method of claim 114 wherein the density of the suspended particles permeated with the suspension medium substantially matches that of the suspension medium.

30 132. The method of claim 114 wherein said perforated microstructures comprise a bioactive agent selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging

agents, cardiovascular agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

133. A respiratory dispersion for the pulmonary delivery of one or more bioactive agents comprising a suspension medium having dispersed therein a plurality of microparticles comprising greater than about 20% w/w surfactant and at least one bioactive agent wherein said suspension medium comprises at least one propellant.

134. The respiratory dispersion of claim 133 wherein said dispersed microparticles comprise greater than about 30% w/w surfactant.

135. The respiratory dispersion of claim 133, wherein said propellant comprises a compound selected from the group consisting of 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane, perfluoroethane, monochlorodifluoromethane, 1,1-difluoroethane and combinations thereof.

136. The respiratory dispersion of claim 133 wherein said propellant is a hydrofluoroalkane propellant.

137. The respiratory dispersion of claim 136 wherein said hydrofluoroalkane propellant comprises 1,1,1,2-tetrafluoroethane.

138. The respiratory dispersion of claim 133 wherein said surfactant is selected from the group consisting of phospholipids, nonionic detergents, nonionic block copolymers, ionic surfactants, biocompatible fluorinated surfactants and combinations thereof.

139. The respiratory dispersion of claim 133 wherein said perforated microstructures comprise a poloxamer selected from the group consisting of poloxamer 188, poloxamer 407, and poloxamer 338.

140. The respiratory dispersion of claim 133 wherein said perforated microstructures comprise oleic acid or its alkali salt.

141. The respiratory dispersion of claim 133 wherein said surfactant comprises a lipid.

142. The respiratory dispersion of claim 141 wherein said lipid has a gel to liquid crystal phase transition greater than about 40°C.

143. The respiratory dispersion of claim 141 wherein said lipid is a phospholipid.

144. The respiratory dispersion of claim 143 wherein said phospholipid is selected from the group consisting of dilauroylphosphatidylcholine, dioleoylphosphatidylcholine,

dipalmitoylphosphatidylcholine, distearylphosphatidylcholine, behenoylphosphatidylcholine, arachidoylphosphatidylcholine and combinations thereof.

145. The respiratory dispersion of claim 133 wherein said microparticles comprise perforated microstructures.

5 146. The respiratory dispersion of claim 145 wherein said perforated microstructures comprise hollow porous microspheres.

147. The respiratory dispersion of claim 146 wherein said hollow porous microspheres have a mean aerodynamic diameter between about 0.5 to 5 μm .

10 148. The respiratory dispersion of claim 133 wherein the mean geometric diameter of the microparticles is between 1 and 5 μm .

149. The respiratory dispersion of claim 133 wherein said bioactive agent is selected from the group consisting of antiallergics, bronchodilators, pulmonary lung surfactants, analgesics, antibiotics, leukotriene inhibitors or antagonists, antihistamines, antiinflammatories, antineoplastics, anticholinergics, anesthetics, anti-tuberculars, imaging agents, cardiovascular
15 agents, enzymes, steroids, genetic material, viral vectors, antisense agents, proteins, peptides and combinations thereof.

150. The stable respiratory dispersion of claim 133 wherein said bioactive agents are selected from the group consisting of budesonide, fluticasone propionate, salmeterol, formoterol and DNase.